Endothelial dysfunction in people with depressive disorders: a systematic review and meta-analysis

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Abstract

The study aimed to identify whether people diagnosed with depression have endothelial dysfunction, assessed by the technique of flow-mediated dilation (FMD), when compared to controls without depression. In addition, to verify whether people with depressive symptoms have impaired endothelial function when compared to controls without symptoms. Also to explore the potential moderators of the association between depression and endothelial dysfunction. Systematic review and metaanalysis. We searched PubMed, PsycINFO, Embase and Web of Science, from inception to April 16, 2021, for studies in people with depression and controls evaluating endothelial function through FMD. The primary outcome was the percentage of change in FMD. Comparative random effects meta-analysis, calculating the mean difference (MD) of the FMD between depressed and controls was performed. Potential sources of heterogeneity were explored by meta-regressions and subgroup analyses. The study protocol was registered with PROSPERO (CRD42020192070). Nine studies evaluating 1,367 participants (379 depressed and 988 controls) (median age=39.8 years, 44.9% men) were included. People with depression had lower FMD=- 1.48% (95%CI=-2.62 to –0.33). High density lipoprotein (HDL) cholesterol levels moderated the effect (beta=-0.408, 95%CI=-0.776 to -0.040). Differences in FMD were found when assessment was done in the first minute after release of the occlusion, when using occlusion position in distal forearm, and when using occlusion pressure between 250 and 300 mmHg. Those with clinical depression (established by diagnostic instruments) presented the greatest dysfunction. Individuals with depression have a more impaired endothelial dysfunction when compared to controls. HDL cholesterol levels and differences in FMD assessment modalities moderate the difference.

1. Introduction

Depression, or major depressive disorder, is a mood disorder that leads to impaired neurovegetative, psychomotor, and cognitive functioning (Fu et al., 2019). It is a highly prevalent disorder, with a point prevalence of approximately 5%; more than 300 million people live with depression worldwide (World Health Organization, 2017). In addition, people with depression are at increased risk of cardiovascular morbidity and premature mortality, resulting in a reduced life expectancy compared to the general population (Correll et al., 2017).

One of the potential mechanisms explaining the increased risk of developing cardiovascular diseases in people with depression might be related to endothelial dysfunction (Maruhashi et al., 2018). Endothelial dysfunction is a marker of preclinical atherosclerosis characterized by impaired endothelium-dependent vasodilation and a procoagulant and proinflammatory state (Daiber et al., 2016; Maruhashi et al., 2018) that is associated with a higher risk of incident cardiovascular diseases (Matsuzawa et al., 2015a), therefore, evaluating endothelial function in people with depression might help identifying those at a higher risk of developing cardiovascular diseases. Flow-mediated dilation (FMD) is a non-invasive technique widely used to assess endothelial dysfunction and measures changes in the endothelium-dependent vasodilator response after shear stress and the dilation induced by the release of nitric oxide (Maruhashi et al., 2018). The endothelial function is assessed by high-resolution ultrasound, where the images of the brachial artery are obtained after mechanical ischemia caused by the inflation of a blood pressure cuff (Thijssen et al., 2019).

To the best of our knowledge, two previous reviews have summarized the literature on endothelial dysfunction in people with depression before. First, a systematic review and meta-analysis including 12 studies involving 1,491 participants with clinical or subclinical depressive symptoms in healthy adults and cardiovascular patients identified a weak correlation between depressive symptoms and endothelial dysfunction ($r=0.19$) (Cooper et al., 2011). Second, a meta-analysis including 13 studies involving 937 patients with depressive symptoms and 5,890 controls without depressive symptoms demonstrated that people with depressive symptoms have a lower FMD when compared to controls (WMD=-2.554, 95%CI=-3.709 to -1.399, $p < 0.001$) (Wu et al., 2018). However, both of these reviews included a study in which the participants had a history of depression (average time since the last episode of about ten years), but were not

depressed at the time of FMD assessment (Wagner et al., 2006). FMD responses are potentially associated with depressive symptom severity (Kalkman, 2020). Also, the previous reviews included studies in people with comorbid cardiovascular diseases associated with endothelial dysfunction (Cooper et al., 2011; Wu et al., 2018). Therefore, the inclusion of these studies in previous reviews may lead to an imprecision on the association.

Thus, this study aimed to: 1) compare endothelial dysfunction, assessed by the technique of flow-mediated dilation (FMD), of people with depression compared to controls without depression; and 2) to explore the potential moderators of the association between depression and endothelial dysfunction.

2. Methods

2.1 Search strategy and selection criteria

We did a systematic review and meta-analysis following the Preferred Reporting items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati et al., 2009). The study protocol was registered with PROSPERO (CRD42020192070).

2.2 Searches

Searches were carried using the following databases: Embase, PubMed, PsycINFO, and Web of Science and used keywords involving the terms related to major depressive disorder and endothelial dysfunction. The search was carried out since database inception to April 16, 2021 (e.g.: PubMed (Vascular dysfunction OR endothelial function OR flow-mediated vasodilation OR Endothelium[mesh] OR Vasodilation[mesh] OR Endothelium-Dependent Relaxing Factors[mesh]) AND (Depression[mesh] OR Depressive Disorder, Major[mesh] OR mood disorder[mesh])). Manual searches of reference lists of included articles and other reviews on the topic were also carried out (Cooper et al., 2011; Wu et al., 2018).

After removing duplicates, two independent reviewers (AJW, EB) selected the possible articles to be included by reading the titles and abstracts. Subsequently, a complete reading of potentially eligible articles was carried out by the same independent reviewers. The cases of disagreement between these reviewers were decided by a third reviewer (FBS).

2.3 Inclusion criteria

Studies with the following attributes were included in the present review: 1) clinical trials (baseline data only), longitudinal cohorts, transversal and case-control, written in Portuguese, English, or Spanish; 2) Studies with people with major depressive disorder, diagnosed according to DSM IV or V criteria (American Psychiatric Association, 2013), or through cutoff of screening instruments established in the literature (e.g.: Hamilton Scale (Hamilton, 1967), Beck Depression Inventory (Beck, 1961) or another); 3) Have evaluated endothelial function by high-resolution ultrasound of the brachial artery by FMD. We used FMD to assess because it is a widely used non-invasive technique, with a good correlation with coronary endothelial dysfunction (Denollet et al., 2018; Matsuzawa et al., 2015a). The study did not include articles that involved other mental disorders (e.g.: bipolar mood disorder, schizophrenia), which evaluated individuals with cardiovascular disease, conference abstracts, review articles, or articles that were not available in full.

2.4 Data extraction

Two reviewers (AJW, EB) extracted data using a standardized form. The data extracted were: first author, year of publication, country of study, number of study participants, age, body mass index (BMI), sex, other cardiovascular risk factors (hypertension, dyslipidemia, triglyceride levels, total cholesterol, high-density lipoprotein (HDL), blood glucose, systolic blood pressure (SBP), diastolic blood pressure (DBP)), smoking, physical activity, depression assessment (clinical diagnosis or use of screening instruments), percentage of change in FMD together with the standard deviation, percentage of change after sublingual nitroglycerin, pressure, and position of brachial artery occlusion and the measurement time of the FMD after the release of the occlusion. We contacted the authors of studies that did not present all available information.

2.5 Risk of bias assessment

The risk of bias of the included studies was assessed by two independent reviewers (AJW, ARB) using the Newcastle-Ottawa (NOS)(Wells, n.d.) scale for cases and controls. The scale consists of three different domains: Selection of participants (four items to be evaluated: the definition of the appropriate case, representativeness of the cases, selection of controls, definition of controls); Comparability (of cases and controls

based on the design or analysis); Exposure (two items to be assessed: determination of exposure and non-response rate). Each item in the participants' selection and outcome/exposure domains receives a point. The comparability domain can receive up to two points, with the maximum score on the scale being nine points (Wells, n.d.). Studies which obtained scores from zero to three were considered low quality, from four to six moderate quality, and from seven to nine points high quality, as used in other studies (Schuch et al., 2019).

2.6 Meta-analysis

Two comparative random effects meta-analysis, using the Dersimonian and Laird were performed. The first one comparing the mean differences and standard deviation of FMD, and the second one comparing the endothelium-independent vasodilation, of people with depression with non-depressed controls. For this, the mean difference (MD) and the 95% confidence interval were calculated. Heterogeneity was assessed using I^2 statistics for each analysis. We considered heterogeneity higher than 50% as substantial heterogeneity (Higgins and Green, 2011). When significant, heterogeneity was explored through meta-regressions, and subgroup analyses. Meta-regressions included as potential moderators investigated: age, BMI, percentage of men, percentage of smokers, triglyceride levels, total cholesterol, HDL, blood glucose, SBP, and DBP. Potential moderators were chosen based on previous studies (Matsuzawa et al., 2015b; Sprung et al., 2013). Subgroup analyses investigating the method of assessing depressive disorder (clinical diagnosis or screening instrument), the position and pressure of brachial artery occlusion, and the measurement time of the FMD were performed. The presence of publication bias was investigated with the Begg-Mazundar Kendall (Begg and Mazumdar, 1994), and the Egger tests (Egger et al., 1997). When tests indicate the presence of publication bias, the Duval and Tweedie (Duval and Tweedie, 2000) trim and fill technique was applied to correct the bias and recalculate the new effect. The N fail-safe test (Rosenberg, 2005) was applied to estimate how many studies would be needed to make the effect non-significant. Analyses were performed using Comprehensive Meta-Analysis version 3.0., by two reviewers (FBS, AJW).

3. Results

3.1 Search results

The initial search resulted in 5,484 publications and, after removing the duplicates, 4,496 titles and abstracts were analyzed. In the next stage, 68 studies were read in full and of these, 60 were excluded, leaving eight studies that met the inclusion criteria of the present review for analysis. The manual search in the references of the eight studies (Broadley et al., 2002; Broadley et al., 2006; Chen et al., 2011; García et al., 2011; Pizzi et al., 2008; Rajagopalan et al., 2001; van Sloten et al., 2014; Zhuo et al., 2011) included and in other reviews on the topic resulted in the eligibility of one more study (Taylor et al., 2006), leaving nine included studies, as shown in figure 1.

We included a total of 1,367 participants (379 depressed and 988 controls) from 9 unique studies. The participants median age was of 39.8 years, with a median of 44.9% men. In four studies (Broadley et al., 2002; Broadley et al., 2006; García et al., 2011; Rajagopalan et al., 2001) the diagnosis of depression was made using diagnostic interviews while five (Chen et al., 2011; Pizzi et al., 2008; van Sloten et al., 2014; Taylor et al., 2006) used screening questionnaires. The FMD assessment protocol varied between the studies included in this review. Further details of included studies are given in table 1. Of the nine studies included, five were considered moderate quality (Chen et al., 2011; Rajagopalan et al., 2001; van Sloten et al., 2014; Zhuo et al., 2011; Taylor et al., 2006) and four high quality (Broadley et al., 2002; Broadley et al., 2006; García et al., 2011; Pizzi et al., 2008). The average of the NOS scale was 6.11.

3.2 Endothelial dysfunction in people with depression versus controls

People with depression have impaired FMD when compared to controls, with a 1.9% (95%CI -3.12 to -0.72) less dilation (figure 2A). The Begg-Mazumdar Kendall test (Tau=-0.14, p=0.60) did not identify publication bias, however, the Egger test did (intercept=-2.64, p=0.04). The Duval and Tweedie technique corrected the funnel plot and estimated that two studies were missing (MD=-1.48, 95%CI=-2.62 to –0.33). The fail-safe N test demonstrated that 129 studies with negative results would be needed to make the difference insignificant.

The summary of the seven studies that evaluated endothelium-independent vasodilation demonstrated that there is no difference between people with depression and controls (MD=-0.69, 95%CI -1.79 to -0.41, P<.218, I^2=61.53; figure 2B).

3.3 Moderators of endothelial dysfunction in people with depression

Age, BMI, percentage of men, percentage of smokers, triglyceride levels, total cholesterol, HDL, blood glucose, SBP and DBP were investigated, through meta-regressions, as potential moderators of endothelial function in people with depression. We have not found sufficient data to explore the role of physical activity as a mediator. HDL levels explained 45% (MD=-0.408, 95%CI=-0.776 to -0.040, *P*=.029) of the difference found between depressed and controls, with a negative association, in which higher levels of HDL were associated with worse endothelial function (table 2).

Subgroup analyses revealed that people who had their depression confirmed through diagnostic instruments showed larger impairment in endothelial function with 3% (95%CI -5.415 to -1.264) less dilation. People with depressive symptoms showed no difference in FMD when compared to controls. Also, in the studies that evaluated FMD in the first minute after the release of the occlusion, there was a difference (MD=-3.090, 95%CI -4.777 to -1.404) between depressed and controls. There is a difference in endothelial function when using the occlusion position in the distal forearm (MD=-4.390, 95%CI -6.607 to -2.172), and when using an occlusion pressure between 250 and 300 mmHg (MD=-2.445, 95%CI -4.274 to -0.616) (table 3).

4. Discussion

The present meta-analysis demonstrates that people with depression have an impaired endothelial function assessed by FMD compared to controls. High heterogeneity was found between the studies, which was explored by meta-regressions and subgroup analyses. The FMD of people diagnosed with clinical depression (established by diagnostic instruments) is significantly different from people without depression. In contrast, people with elevated levels of depressive symptoms as assessed with screening instruments but with no clinical diagnosis have no different endothelial function compared to controls.

We found that people with depression had a 1.4% lower dilating response when compared to controls. Our findings corroborate the direction of previous studies demonstrating a link between depression and endothelial dysfunction (Cooper et al., 2011; Wu et al., 2018), however, in previous studies, individuals with a history of

depression, but free from depression at the moment of the assessment, and with cardiovascular diseases were included. The inclusion of these studies might lead to imprecisions on the estimate since, for example, in the study of Wagner et al. (2006), the time since the last episode was 10 years before FMD assessments. Once it is expected that depression is associated with FMD, the inclusion of this study may underestimate the difference between those with depression and controls. On the other hand, the inclusion of studies in which the participants had comorbid cardiovascular diseases might result in an exacerbated difference since it is expected that people with cardiovascular diseases have altered FMD.

In the present study, we advanced the field showing that people with depressive symptoms, but not necessarily with clinical depression, might not have an impaired endothelial function, while people with clinical depression have a greater dysfunction, corresponding to 3% lower dilation. This can be associated with a 36% increase in the risk of developing cardiovascular disease, considering that a previous meta-analysis, when assessing the prognostic value of FMD as a predictor of cardiovascular outcomes, found that the adjusted relative risk for cardiovascular outcomes for every 1% increase in FMD was 0.88 (95% CI 0.84 – 0.91) (Matsuzawa et al., 2015b). In other words, a reduction of 1% in FMD is associated with a 12% increase in the risk of developing cardiovascular diseases (Matsuzawa et al., 2015b).

There might be several underlying mechanisms related the impaired endothelial function in people with depression. First, people with depression have a higher risk for dyslipidemia and obesity and both dyslipidemia and obesity are associated with a higher risk for atheromatous lesions or atheromas in arterial walls (Polanka et al., 2018). This is supported by our meta-regressions showing an inverse association between HDL and endothelial function, in which higher levels of HDL were associated with worse endothelial function. The protective effects of HDL on blood vessels are well-established in the literature and include stimulating the release of nitric oxide, reducing the inflammatory response and stimulating endothelial repair, however, the protective effects of HDL seem to be limited in people with diabetes, metabolic syndrome, and coronary artery disease (Takaeko et al., 2019). Second, people with depression present a pro-inflammatory state, with increased levels of pro-inflammatory cytokines, adhesion molecules, and circulating acute phase proteins, which, in turn, contributes to the malfunction of several neurotransmitters and hormonal systems, resulting in inflammatory diseases (Gazal et al., 2015). Another possible explanation for the

difference between people with depression and controls may be a difference in lifestyle habits and health behaviors, as people with depression tend to have a worse lifestyle, with poor eating habits, smoking, obesity, excessive alcohol consumption (Rahe et al., 2016) and lower levels of physical activity and fitness (Schuch et al., 2017; Schuch et al., 2019). Finally, this increased risk may be due to non-adherence to pharmacological treatment for existing cardiovascular risk conditions (Polanka et al., 2018). Importantly, the treatment of depression with antidepressants and the practice of physical exercises collaborate to improve depressive symptoms and the endothelial function of people with depression (Blumenthal et al., 2012; Pizzi et al., 2009).

In the present study, we have found that the magnitude of the FMD varies according to the technique used. In our subgroup analyzes, there is a difference in the endothelial function of depressed people when compared to controls when the FMD measurement is performed in the first minute after the release of the occlusion and no difference when the assessment is performed in other moments (30s, 45s, and others). The use of the one-minute time to estimate the peak FMD has been considered for many years. However, it is known that this time interval can underestimate the peak of dilation and it is recommended that obtaining the FMD be performed with a continuous examination of the diameter brachial artery up to 180 s after the occlusion is released (Thijssen et al., 2019). Also, there was a difference in endothelial function between depressed and controls when the brachial artery occlusion was performed in the distal portion of the forearm, which was not observed when the occlusion was performed in the proximal portion of the forearm or the forearm without specifying the portion, suggesting that the occlusion position can influence the magnitude, duration, and nature of the dilating response. This is in line with previous studies that show that the use of proximal occlusion can collapse the artery leading to an inaccurate assessment; also, in this location (proximal), the dilating response can be mediated by substances other than nitric oxide (Thijssen et al., 2019). Lastly, there was a difference in the endothelial function of depressed and controls with the use of occlusion pressure between 250 and 300 mmHg. Despite the widespread use of occlusion pressure between 200 and 300 mmHg, it is recommended that an occlusion pressure greater than 50 mmHg be used above SBP so that arterial inflow does not occur (Thijssen et al., 2019).

Our data did not identify differences in endothelium-independent vasodilation in people with depression when compared to controls. Thus, the impaired independent endothelial response may reflect functional changes in smooth muscle cells or structural

changes in blood vessels, causing impairments in the dilation of these vessels, which may be related to the increased development of atherosclerosis and consequently the increase in cardiovascular risk (Maruhashi et al., 2018).

Endothelial damage that results in impaired endothelial function is one of the first changes found in atherosclerosis (Narita et al., 2007). In a study by Broadley et al. (2002), endothelium-independent vasodilation was normal in people with depression compared to controls, while the dependent endothelial response was altered. It is possible that the reduction in FMD, without impairing vascular smooth muscle function, is consistent with an early stage of atherosclerosis in individuals with depression (Narita et al., 2007). This impairment of FMD, as an early marker and subclinical evaluation of cardiovascular disease, may be a predictor risk factor even in the absence of a diagnosis of heart disease (Shechter et al., 2014).

Limitations

The current findings need to be interpreted in light of some limitations. First, the small number of studies included and the variability in the amount of information available in each study made it impossible to explore heterogeneity in more detail. It was, for example, not possible to assess how much the chronicity and severity of depression are related to endothelial function. Also, it was also not possible to explore how lifestyle factors and the use of antidepressant medications are related to endothelial function in people with depression. For example, information on the use of antidepressant drugs was quite heterogeneous. In studies in which the participants had depressive symptoms (N=5), two studies reported that the participants used antidepressants. However, without informing which type of medication (tricyclics or selective serotonin reuptake inhibitors or other) was used, and in the others three of them, the participants did not use antidepressant medication (N=1) or not informed if participants were taking or not (N=2). In the studies in which the participants were diagnosed with depression (N=4), in three of them, the individuals did not use antidepressant medications and, in the study in which they used it, different types of medications were used. Second, due to the design of the (cross-sectional) studies, it was not possible to establish causality.

Conclusions

In conclusion, individuals with depression have endothelial dysfunction when compared to controls without depression. The mechanisms responsible for this change are uncertain. Our findings may have clinical implications, as they suggest the consideration of the need to implement endothelial function assessment to potentially prevent cardiovascular diseases in people with depression.

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Tables

Table 1: Characterization of the studies and the FMD protocol

Study	Country	Design	Sample size		% of men		Mean age		Potential moderators	Diagnosis/ *screening*	FMD parameters		
			Cases (N)	Controls (N)	Cases (%)	Controls (%)	Cases	Controls			Occlusion position	Occlusion pressure	FMD time
Broadley et al. 2002	United Kingdom	case-control	12	10	50	80	39	35	BMI; Total cholesterol; SBP; DBP	Diagnosis (DSM-IV)	forearm (distal)	above SBP	60 s
Broadley et al. 2006	England	randomized clinical trial	30	36	27	47	40.1	39.5	BMI; Triglycerides; Total cholesterol; HDL; Blood glucose; Percentage of smokers; SBP; DBP	Diagnosis (DSM-IV + CID-10)	forearm (distal)	250 a 300 mmHg	60 s
Chen et al. 2011	China	case-control	41	88	46	40	55	54	BMI; Triglycerides; Total cholesterol; HDL; Blood glucose; Percentage of smokers; SBP; DBP	Screening (DASS 21 ≥ 8)	forearm	250 mmHg	60 s
Garcia et al. 2011	Colombia	case-control	50	50	32	32	22.6	23.4	BMI; Triglycerides; Total cholesterol; HDL; Blood glucose; Percentage of smokers; SBP; DBP	Diagnosis (DSM-IV) + Zung	forearm (proximal)	300 mmHg	60 s
Pizzi et al. 2008	Italy	case-control	96	319	49	51.7	57.1	57.7	BMI; Triglycerides; Total cholesterol; HDL; Blood glucose; Percentage of smokers; SBP; DBP	Screening (BDI ≥ 10)	forearm (distal)	300 mmHg	De 10 a 120 s

(Table continues on next page)

Study	Country	Design	Sample size		% of men		Mean age		Potential moderators	Diagnosis/ *screening*	FMD parameters		
			Cases (N)	Controls (N)	Cases (%)	Controls (%)	Cases	Controls			Occlusion position	Occlusion pressure	FMD time
(Continued from previous page)													
Rajagopalan et al. 2001	EUA	case-control	15	15	27	27	29	31	BMI; Triglycerides; HDL; Percentage of smokers; Blood glucose; SBP; DBP	Diagnosis (DSM-IV)	forearm (proximal)	200 mmHg	60 s
Sloten et al. 2014	Holanda	Cross-Sectional	63	430	38.1	51.9	71.1	69.2	BMI; Triglycerides, Total cholesterol; HDL; Percentage of smokers; SBP; DBP	Screening (CES-D ≥ 16)	forearm	100 mmHg above SBP	45, 90, 180 e 300 s
Taylor et al. 2006	EUA	case-control	48	20	33	60	62.3	62.5	BMI; Triglycerides; Total cholesterol; HDL; Percentage of smokers; SBP; DBP	Screening (BDI + Hamilton)	forearm	50 mmHg above SBP	30, 45 e 60 s
Zhuo et al. 2011	China	case-control	24	20	62.5	70	31.6	27.8	BMI; Triglycerides, Total cholesterol; HDL; Blood glucose; Percentage of smokers	Screening (BDI + HDRS)	forearm (proximal)	50 mmHg above SBP	30 s a 120 s

Abbreviations: BMI: Body mass index; BDI: Beck Depression Inventory; CES-D: Center for Epidemiological Scale Depression; DBP: diastolic blood pressure; HDL: high density lipoprotein; HDRS: Hamilton Rating Scale for Depression; SBP: systolic blood pressure.

Table 2*:* Meta-regressions of potential FMD moderators in people with depression

Moderator	N	Beta coefficient	CI 95%	*P* value	R^2
Age	9	0.007	-0.108 to 0.123	.900	0.00
% men	9	-0.013	-0.135 to 0.109	.833	0.00
BMI	9	0.061	-0.728 to 0.851	.878	0.00
% smokers	8	0.024	-0.120 to 0.169	.741	0.00
Triglycerides	8	0.027	-0.030 to 0.084	.351	0.00
Total cholesterol	8	-0.007	-0.090 to 0.076	.866	0.00
HDL	**8**	**-0.408**	**-0.776 to -0.040**	**.029**	**0.45**
Blood glucose	6	0.042	-0.374 to 0.459	.841	0.00
SBP	8	0.042	-0.089 to 0.175	.525	0.00
DBP	8	0.008	-0.360 to 0.376	.966	0.00

Abbreviations: BMI: Body mass index; CI: Confidence interval; DBP: Diastolic blood pressure; HDL: High density lipoprotein; SBP: Systolic blood pressure.

Table 3: Subgroup analyzes

Variable	N	MD	CI 95%	*p* valor	I^2
Diagnosis or Screening					
Diagnosis	**4**	**-3.33**	**-5.415 to -1.264**	**.001**	**89.3**
Screening	5	-1.232	-2.643 to 0.179	.087	94.7
Occlusion pressure					
50 mmHg above SBP	2	-0.406	-3.126 to 2.314	.770	33.3
100 mmHg above SBP	1	-0.01	-3.337 to 3.317	.995	0
200 mmHg	1	-5.78	-12.222 to 0.662	.079	0
250 a 300 mmHg	**4**	**-2.445**	**-4.274 to -0.616**	**.008**	**87.1**
FMD time					
1 minute	**5**	**-3.090**	**-4.777 to -1.404**	**<.001**	**85.7**
Other moments	4	-0.892	-2.399 to 0.615	.246	95.1
Occlusion position					
Forearm (unspecified)	3	-1.305	-3.375 to 0.764	.216	86.9
Forearm (distal)	**3**	**-4.390**	**-6.607 to -2.172**	**<.001**	**80.1**
Forearm (proximal)	3	-0.202	-2.466 to 2.062	.861	61.8

Abbreviations: CI: Confidence interval; FMD time: Time of FMD measurement after occlusion release; MD: Mean difference; SBP: Systolic blood pressure.